REMARKS

Claims 1, 2, 18, 19, 23-36, and 46-59 are pending in the present application. New claims 60-69 are added. Support for the new claims is found throughout the specification, e.g., at page 3, lines 22-25, page 12, lines 3-8, and page 12, line 23-page 17, line 8.

35 USC § 103 (a)

Gupta et al.

All of the claims have been rejected in view of Gupta et al. (EMBO J. 15:2760-2770, 1996) in combination with other art. For claims 1, 2, 18, 19, and 49-59, Gupta et al. is cited for disclosing "the identification of JNK isoforms, including JNK3 from adult human brain cells (neuronal cells)..." (Office Action at page 3, first full paragraph with reference to claims 1, 2, 18, and 19; see also page 9, first paragraph with reference to claims 49-59).

Applicants respectfully disagree with the basic premise in the Office Action that presence of a sequence in a library obtained from whole brain indicates neuronal expression. Gupta et al. merely shows that JNK3 cDNA is present in libraries prepared from brain. As confirmed by Roger Davis, Ph.D. (a co-author of Gupta et al. and a co-inventor of the present application) in his Declaration (Exhibit A), Gupta et al.'s cDNA libraries were constructed using whole brain preparations and thus contained cDNA from not only neuronal cells, but also from other cell types such as glia. In particular, applicants note that there are between 10 and 50 times more glial cells than neurons in the central nervous system (Kandel and Schwartz, Principles of Neural Science, Second Edition, Elsevier, New York, 1995, p. 17, copy enclosed at Exhibit B).

Gupta et al. shows only that JNK3 was present in brain libraries. Thus, it cannot be concluded from Gupta et al. that JNK3 is expressed in neuronal cells. Such a conclusion is not supported by the facts in the reference. Therefore, applicants contend that Gupta et al. cannot supply the elements of the claims related to the presence of JNK3 expression or activity in a neuronal cell (claims 1, 2, 18, 19, and 49-59).

Neither Gupta et al. nor any of the other cited references show that JNK3 is expressed in neuronal cells. Claims 1, 2, 18, 19, and 49-59 recite that a neuronal cell be contacted with a test compound or that JNK3 expressed and isolated from a neuronal cell be used. Thus, the art cited

in the Office Action is not sufficient to establish a *prima facie* case of obviousness because one of the claim elements is completely absent from the prior art.

Gupta et al. is also cited against claims 23-36 and 46-48. This rejection, as well as the other rejections are discussed in greater detail below.

Claims 1, 2, 18, and 19 are rejected for alleged obviousness over McKay et al. (U.S. Patent No. 5,877,309, issued March 2, 1999, filed August 13,1997) in view of Gupta et al. (EMBO J. 15:2760-2770, 1996) and Sawyer et al., (Molecular Biology and Biotechnology, A Comprehensive Desk Reference, Ed. Robert A. Myers, 1995, Wiley-VCH, USA, pp. 648-653). Applicants respectfully disagree with the rejection. The Office Action also cites Uhlmann et al. (Molecular Biology and Biotechnology, A Comprehensive Desk Reference, Ed. Robert A. Myers, 1995, Wiley-VCH, USA, pp.38-45).

To establish a *prima facie* case of obviousness, there must be 1) some suggestion or motivation in the references or the art to combine the references, 2) there must be a reasonable expectation of success, and 3) the combined references must teach or suggest all the claim limitations. Applicants respectfully maintain that the cited references do not meet the requirements for establishing a *prima facie* case of obviousness.

Claim 1 is drawn to a method of identifying whether a test compound modulates JNK3 expression. The method includes incubating a neuronal cell that can express a JNK3 protein with a compound and comparing JNK3 expression in the presence of the compound to expression in the absence of the compound. Claims 2, 18, and 19 depend from claim 1.

The Office Action states "McKay et al. teach a method for assaying modulation of expression of JNK including JNK1, JNK2, and JNK3" and oligonucleotides (Office Action at page 2). The Office Action also states "McKay et al. teach that such oligonucleotides can be used to for [sic] inhibiting hyperproliferation of cells and formation, development and maintenance of tumors." The Office Action admits that McKay et al. does not specifically teach a peptide, peptidomimetic, small organic molecule, or small inorganic molecule. Furthermore, McKay says nothing about JNK expression in a neuronal cell.

The Office Action seeks to supply deficiencies of McKay et al. by citing Gupta et al. stating "Gupta et al. teach the identification of JNK isoforms, including JNK3 from adult human

brain cells (neuronal cells) and express such JNK isoforms in CHO cells" (Office Action at page 3, first full paragraph). Applicants disagree with this statement. As discussed above, Gupta et al. merely shows that JNK3 RNA is present in libraries prepared from brain since the brain cDNA libraries used by Gupta et al. were constructed using whole brain preparations and thus contained cDNA from not only neuronal cells, but from other cell types such as glia. Therefore, it cannot be concluded from Gupta et al. that JNK3 is expressed in a neuronal cell. Such a conclusion would constitute impermissible hindsight. Thus, the combination of McKay et al. and Gupta et al. does not satisfy the all elements requirement for a *prima facie* case of obviousness.

Uhlmann et al. is cited for a discussion of the use of oligonucleotides. Nothing in Uhlmann et al. mentions a JNK much less that JNK3 is expressed in a neuronal cell. Similarly, Sawyer et al. is cited to support the contention in the Office Action that the use of peptides and peptidomimetics for treatment of disorders involving enzymes and receptors is well known in the art. Nothing in Sawyer et al. mentions a JNK much less expression of JNK3 in a neuronal cell. Thus, neither Uhlmann et al. nor Sawyer et al. can provide the deficiencies of McKay et al. and Gupta et al., namely, the expression of JNK3 in a neuronal cell. Since no combination of these references can supply all elements of claims 1, 2, 18, or 19, applicants believe that the claims are not made obvious by the combination of references.

The Office Action repeats portions of applicants' earlier arguments rebutting the assertion that a *prima facie* case was established by the June, 2002 Office Action's citation of only McKay. As previously pointed out by applicants, McKay does not disclose or suggest the use of neuronal cells for methods of assaying modulation of expression of JNK proteins as required by the pending claims, and the reference is primarily concerned with the diagnosis and therapy of tumor formation and metastasis. Furthermore, McKay et al. does not disclose anything related to the expression of JNK3 in a neuronal cell. In response to the previous Response by applicants (dated December 13, 2002), the present Office Action has included Gupta et al. in the rejections for obviousness as well as Uhlmann et al. and Sawyer et al.

As discussed above, the addition of Gupta et al. to McKay et al. does not provide all of the elements of the claims, e.g., the expression of JNK3 in a neuronal cell. Furthermore, nothing in either McKay et al. or Gupta et al. teaches screening peptides, peptidomimetics, small non-

nucleic acid organic molecules, or small inorganic molecules for their ability to modulate JNK3 expression.

Furthermore, just because Gupta et al. identified the presence of JNK3 in brain libraries, it doesn't suggest the use of a neuronal cell to express JNK3 in a method of screening using any type of compound. Applicants note that the oligonucleotides used by McKay et al. were designed to hybridize to a JNK nucleic acid sequence. Thus, McKay et al. was merely assaying for the activity of oligonucleotides known to hybridize to the target nucleotides. Applicants are claiming a screening method, in which a compound which is a peptide, a peptidomimetic, a small organic molecule, or a small inorganic molecule is tested in a neuronal cell for the ability to modulate JNK3 expression.

The Office Action cites Uhlmann et al. to illustrate drawbacks to the use of oligonucleotides. Applicants are not claiming the use of oligonucleotides and so the reference is of no direct relevance. The Office Action argues, citing Uhlmann et al. to support the argument, that one in the art would be motivated to use something other than oligonucleotides because it is "well-known in the art that the method of using antisense oligonucleotides suffers from inherent drawbacks..." (Office Action at page 3, second full paragraph). Nothing in the Uhlmann et al. reference suggests that one resort to the use of some type of agent other than an oligonucleotide. The reference provides information for improving the use of oligonucleotides. It does not suggest that they should not be used, and in fact the reference discusses successful uses of oligonucleotides. Furthermore, applicants point out that McKay et al. successfully used an oligonucleotide to modulate expression of a JNK. It would seem most consistent with the reasoning of the Office Action that if the art reported the successful use of an oligonucleotide (as in McKay et al.), and Uhlmann et al. provides even more instruction for how to use oligonucleotides, then one would not look to alternative agents that can modulate JNK expression.

Next, the Office Action cites Sawyer to support the statement that the use of peptides and peptidomimetics for treatment of disorders involving enzymes and receptors is well known in the art. Claim 1 is drawn to a method of identifying a compound that modulates JNK3 expression. Sawyer does not discuss applications of peptides or peptidomimetics that affect expression. Instead, Sawyer discusses the use of peptides or peptidometics to affect activity. Sawyer also

lists peptides, e.g., at Table 1 (page 650). Although Sawyer may show that peptides were known in the art, the fact remains that there is nothing in Sawyer to suggest any connection with JNK3 and certainly nothing to suggest the use of peptides or peptidomimetics in a screening method to identify compounds that modulate JNK3 expression.

The Office Action (at page 3) combines McKay et al. and Gupta et al. stating

> it would have been obvious to one of ordinary skill in the art, to identify agents other than oligonucleotides that modulates [sic] the expression of JNK3 in neuronal cells, either in order to increase the number of agents become available for such use or to overcome the disadvantages of the method of using antisense oligonucleotides.

This statement is followed by the citation of Uhlmann et al. (paragraph bridging pages 3 and 4) and Sawyer et al. These references are cited to support the statement.

As discussed above, the Office Action provides no reason why one in the art, knowing that McKay has successfully used oligonucleotides to modulate expression of a JNK, would ever turn to the art to seek an alternative agent. Nor is it even apparent that one in the art, after reading Uhlmann et al., which, while discussing issues related to the use of oligonucleotides, teaches methods of improving their use and does not suggest using other types of agents, would turn to the use of an agent other than an oligonucleotide.

In view of the above arguments, applicants submit that neither Uhlmann et al., Sawyer et al., or both, even combined with McKay et al. and Gupta et al. provide any motivation for one in the art to seek agents (aside perhaps, from oligonucleotides) that would modulate JNK3 expression. Accordingly, in view of the foregoing, applicants believe that the combination of McKay et al., Gupta et al., Uhlmann et al., and Sawyer et al. do not provide all of the elements of claims 1, 2, 18, and 19, nor do they provide any suggestion or motivation for one in the art to combine the references. Therefore, the combination of cited references cannot make obvious the invention of claims 1, 2, 18, and 19.

Claims 49-59 are rejected as being unpatentable over Gupta et al. (EMBO J., 15:2760-2770, 1996) and McKay et al. (U.S. Patent No. 5,877,309). The rejection is reiterated from previous Office Action dated June 16, 2003. Claims 49-59 are drawn to a method of identifying

candidate compounds for treatment of disorder related to excitotoxicity or a neuronal disorder. The method involves the use of either a neuronal cell that can express a JNK3 protein under conditions sufficient to express the JNK3 protein or a JNK3 protein that is expressed and isolated from a neuronal cell. JNK3 activity is assayed in the presence and absence of a compound. Applicants do not believe that the cited references provide all elements of the claims nor do they provide any suggestion or motivation for combining the references to make the claimed invention.

The Examiner asserts "Gupta et al. provides assay methods for determining the activity and binding of JNK3 to its substrate." (Office Action at page 6, second full paragraph). The Office Action also states "[t]he reference does not teach the use of the same methods towards identification of compounds that modulate the activity" (Office Action at page 6, second full paragraph). Applicants assume that this means that the reference does not teach the same methods as those disclosed in the specification.

As discussed above, Gupta et al. discloses the detection of JNK3 in brain libraries (i.e., cDNA). As discussed in the Declaration by Roger J. Davis (Exhibit A), the libraries contain sequences from various cell types in addition to neuronal cells. Gupta et al. does not disclose the expression of JNK3 RNA by a neuronal cell. Furthermore, Gupta et al. does not even demonstrate the presence of JNK3 protein in a brain cell of any kind much less any JNK activity in a brain cell. The only JNK protein and activity shown in Gupta et al. was in Chinese hamster ovary cells (CHO cells). Therefore, Gupta et al. does not describe or suggest that one could use a neuronal cell to express JNK3. Nor does it provide a reason why one would be motivated to do so.

McKay et al. claims that inhibiting the expression of JNK protein using oligonucleotides leads to inhibition of hyperproliferation of cells and formation, development, and maintenance of tumors. McKay et al. does not describe the expression or activity of any JNK in a neuronal cell. Since neither Gupta et al. nor McKay et al. teach even the presence of JNK3 in a neuronal cell, they certainly do not teach the use of a neuronal cell or a JNK3 from a neuronal cell to assay JNK activity. Therefore, the combination of these references fails to supply or even suggest this element of claims 49-59.

Applicants also point out that at the time of filing, it was most commonly believed that neuronal cells did not proliferate. As discussed above, McKay shows that inhibiting the expression of JNK3 leads to inhibition of hyperproliferation of cells and formation, development, and maintenance of tumors. Gupta et al. shows JNK3 activity only in a transformed cell line. Therefore, it is not apparent to applicants why one of ordinary skill in the art would look to McKay et al. or Gupta et al., which relates to tumor cells and proliferation, to be related in any way to a non-proliferating cell type, a neuronal cell.

The Office Action also states (at page 8, second paragraph)

> ...applicants have amended the claims by including the word "neuronal" and also to include the phrase "expressed and isolated from a neuronal cell" and argue that neither Gupta et al. nor McKay et al. describe the identification of modulators of JNK activity in neuronal cells. ...there is not evidence either in the art provided by the applicants that the JNK3 isolated from neuronal cells is any different from JNK3 isolated from other cells. ...Gupta et al. isolate the cDNAs from human brain tissue (neuronal cells) and express the isolated cDNAs in CHO cells (see page 2761, columns 1 and 2).

The Office Action seems to suggest that the cell type in which a gene is expressed makes no difference. The claim recites "incubate a neuronal cell that can express..." The cited art fails to disclose that neuronal cells (as opposed to other brain cells) actually express JNK3. Thus, the prior art fails to provide all of the elements of the claims. No further information is required to refute the rejection.

The Office Action also states (at page 8, first full paragraph)

> applicants may argue that the above rejection is improper as the reference of McKay et al. or Gupta et al. does not teach the involvement of JNK3 in neuronal disorders or that compounds that modulate activity/expression of JNK3 can be used to treat neuronal disorders. Such an argument will not be persuasive to overcome the above rejection because applicants have not established any specific step of the claimed method that requires knowledge of such a relationship between JNK3 and neuronal disorders or JNK3 and excitotoxic disorders in the claims.

Applicants have pointed out that neither McKay et al. nor Gupta et al. even show that JNK3 is expressed in neuronal cells. Applicants' discovery that JNK3 actually plays a role in excitotoxicity (e.g., Examples 3-8 of the specification) provides the motivation for using a neuronal cell and thus provides the relationship required to make the claimed invention. The claimed methods recite the use of either a neuronal cell or a JNK3 obtained from a neuronal cell. Applicants believe that sufficient steps and linkage are provided by the specification and in the claims.

In view of the arguments presented above, applicants believe that the cited references do not provide all the elements of the claims, and that there is no suggestion or motivation to combine the references to make the present invention.

Claims 23-36 and 46-48

The allowability of claims 23-36 and 46-48 has been withdrawn in view of Gupta et al. (EMBO J., 15:2760-2770, 1996), Schwarzschild et al. (J. Neuroscience, 17:3455-3466, 1997), and Meldrum (Brain Res. Rev. 18:293-314, 1993). Applicants respectfully disagree with the rejection.

Claims 23-36 and 46-48 are drawn to a method of identifying a compound that modulates JNK3 expression, activity, binding to a substrate or phosphorylation of JNK3 substrate. The methods all require administering the selected compound to an animal model of excitotoxic disorder and assaying the animal for excitotoxicity. A decrease in excitotoxicity in the animal indicates that the compound modulates excitotoxicity. Applicants submit that the cited references do not supply all of the limitations of the claims and fail to supply any suggestion or motivation to combine the references to make the claimed invention.

As discussed above, Gupta et al. does not demonstrate that JNK3 is expressed in neuronal cells, the cell type in which excitotoxicity originates. Gupta et al. does not mention excitotoxicity and cannot provide any motivation or suggestion for linking excitotoxicity with JNK3 activity.

Schwarzschild et al. shows that glutamate increased the level of JNK activity in striatal cell cultures. Glutamate is a neurotransmitter associated with the induction of excitotoxicity.

The Office Action acknowledges that the reference does not specifically recite that JNK3 is activated.

Applicants contend that Schwarzschild et al. fails to show a connection between the excitotoxic effects of glutamate, which were known in the art, and the ability of glutamate to activate SAPK/JNK. In fact, Schwarzschild et al. shows that activation of JNK by glutamate does not result in cellular toxicity (see, Schwarzschild et al. at page 3464, first column, lines 7-9). Thus, Schwarzschild et al. does not suggest that modulation of JNK3 results in a decrease in a particular type of cellular toxicity, i.e., excitotoxicity. Therefore, Schwarzschild et al. does not describe that glutamate has an excitotoxic effect because it activates SAPK/JNK – in fact, the reference teaches that this is not the case. Thus, Schwarzschild et al. does not provide any motivation or suggestion for one in the art to associate excitotoxicity with JNK3 activity.

Meldrum et al. discusses acidic amino acids and is cited as teaching "in detail amino acids that act as excitotoxins and their contribution to neurodegenerative disorders." (Office Action at page 11, first paragraph). It is also cited as providing animal models. Meldrum et al. provides no information whatsoever about JNK3, much less its presence in a neuronal cell or its role in excitotoxicity. Therefore, Meldrum cannot supply the deficiencies of Gupta et al. and Schwarzschild et al..

The Office Action states (at page 11):

> Combining the teachings of the above three references [Gupta et al., Schwarzschild et al., and Meldrum et al.] it would have been obvious to one of ordinary skill in the art that glutamate is an excitotoxin capable of inducing several types of neuronal damage and over stimulation by high levels of glutamate would also activate JNK kinase including JNK3 which phosphorylates other transcriptional factors and therefore, compounds which inhibit JNK activities such as phosphorylation, binding etc. would in turn inhibit excitotoxic effects of glutamate or related amino acids and that such compounds could be identified by administering a compound which inhibits JNK3 expression/activity *in vitro*, to an animal model of excitotoxic disorder as taught by Meldrum and choosing those that reduce the excitotoxic effects. One of ordinary skill in the art would have been motivated to do so as such identified compounds would be expected to have use as therapeutic agents for excitotoxic disorders. One of ordinary skill in the art would have a reasonable expectation of success since Meldrum

teach the animal model experiments, Gupta et al. teach the assay methods to monitor for JNK activity/expression/binding and phosphorylation and Schwarszchild et al. show the connection between glutamate and JNK.

As discussed above, nothing in any of the three cited references relates JNK3 to a neuronal cell and excitotoxicity. Furthermore, applicants see nothing in the references providing any suggestion or motivation to combine the references, and respectfully suggest that the scheme provided by the Office Action represents impermissible hindsight.

In view of the foregoing, applicants respectfully request that the rejection under 35 U.S.C. § 103 (a) be withdrawn and the pending claims be allowed.

CONCLUSION

Applicants believe that all of the claims are in condition for allowance, which action is requested. Enclosed is a $930.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 10363-005001.

Respectfully submitted,

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